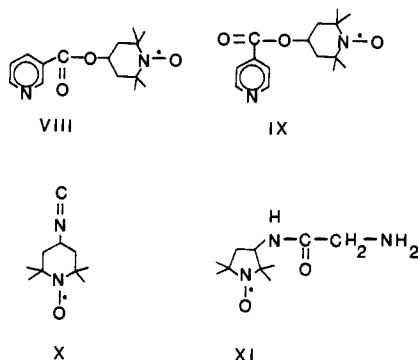


exchange interaction would be expected to be similar if the same ligand were coordinated to VO(hfac)₂ or to the heme in cytochrome P450. When spin-labeled pyridine IX was coordinated to VO(hfac)₂, the value of the exchange coupling constant J was $7 \times 10^{-4} \text{ cm}^{-1}$.⁴⁹ Since the values of J for the VO(hfac)₂ complexes were smaller when the spin labeled substituent was on the 3-position of the pyridine than for the 4-substituted analogue, weaker exchange would be expected for complexes of VIII than of IX.



Therefore the assumption that exchange interaction was negligible for the cytochrome P450 complex of VIII was reasonable.

In ref 5 and 6 it was reported that when isocyanide X coordinated to cytochrome P450 the complex had g values of 2.19, 2.08, and 1.97. These g values are approximately the averages of those obtained for cytochrome P450 bonded to long-chain isocyanides (2.45, 2.30, 1.91) and nitroxyl radicals ($g \sim 2$) which suggests that the spectrum was due to strong exchange interaction between the unpaired electrons on the iron and the nitroxyl. Simulated spectra indicated that $|J| \geq 0.4 \text{ cm}^{-1}$ would be required

to give these average g values. Such a large value of J is reasonable for an isocyanide bridging between the metal and the nitroxyl ring.

When nitroxyl XI was coordinated to cytochrome P450 new signals were reported at $g = 2.047$ and 2.101 .^{6,13} The spectrum shown in Figure 5a of ref 6 also indicated new signals at $g \sim 1.90$ and 1.88 . These features were reproduced by simulated spectra with $r = 7 \text{ \AA}$, $\epsilon = 25^\circ$, and $J = -0.03 \text{ cm}^{-1}$ (the definition of ϵ is given in ref 14). CPK molecular models indicate that the values of r and ϵ are consistent with plausible conformations of the ligand. For this magnitude of J and the large g -value differences between the iron and nitroxyl unpaired electrons, there is little mixing of the iron and nitroxyl wavefunctions. Thus the effect of the exchange interaction on the nitroxyl signal is nearly isotropic, despite the anisotropy in the iron g values. The splitting into signals at 2.047 and 2.101 is due to the contribution from the anisotropic dipolar interaction and thus is quite sensitive to the interspin distance. The iron signals from the spin-labeled complex were not resolved due to overlap with the spectrum of cytochrome P450 that was not coordinated to the spin label. Attempts to simulate the spectrum without exchange interaction were unsuccessful.

The spectra in the literature for spin labels coordinated to the heme in cytochrome P450 provide examples of interaction dominated by exchange interaction (ligand X) or dipolar interaction (ligand VIII) and an example where the two contributions are of comparable magnitude (ligand XI). They provide a good example of the need to consider both contributions when analyzing metal-nitroxyl interactions.

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Deuterium Isotope Effects on Nuclear Shielding. Directional Effects and Nonadditivity in Acyl Derivatives[†]

Poul Erik Hansen,[†] Flemming M. Nicolaisen,[§] and Kjeld Schaumburg*[§]

Contribution from the Institute I, Roskilde University Centre, DK-4000 Roskilde, Denmark, and the Department of Chemical Physics, The H.C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø., Denmark. Received April 8, 1985

Abstract: Deuterium isotope effects on the ¹⁹F and ¹³C nuclear shieldings have been investigated in acyl derivatives. A nonadditivity of the ³ΔF(D) of acetyl fluoride has been experimentally established and related primarily to nonuniform rotamer distributions of the mono- and dideuterated isotopomers. The ³ΔF(D)'s show furthermore a distinct orientational dependence. The isotope effects for the configurations where the nuclei in question are in a trans position are positive and those in which they are gauche are negative. The ²ΔCO(D)'s are negative and additive in all the investigated cases. The observed isotope effects are discussed in general in terms of substituent and vibrational effects.

The interest in isotope effects on nuclear shielding has gradually increased due to the advent of high-field NMR spectrometers.¹ They have with their high sensitivity made possible the observation of isotope effects in many unenriched samples and simultaneously extended the possibility of observing isotope effects due to long-range effects. It has become apparent that many of the observed

effects are of use both for spectral interpretation and for structural elucidation.

The origin of the isotope effect is entirely vibrational. In spite of the advances in vibrational analysis and force constant calculations currently taking place, no accurate interdependence of the long-range isotope effects on chemical shift has been established. The observation of a negative ²ΔCO(D) in acetone² as well as

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[‡] Roskilde University Centre.

[§] University of Copenhagen.

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Table I. Deuterium Isotope Effects^a over Two and Three Bonds in Carbonyl Compounds, CD_nH_{3-n}COX

compd ^b	² ΔCO(D)	X	³ ΔX(D)	¹ ΔC(D)	other
acetone- <i>d</i> ₆	-0.329	¹³ C		0.747	
acetone- <i>d</i> ₅	-0.275				
acetone- <i>d</i> ₄	-0.220			0.501	
acetone- <i>d</i> ₃	-0.170				
acetone- <i>d</i> ₂	-0.111			0.249	
acetone- <i>d</i> ₁	-0.055				
acetophenone- <i>d</i> ₃	-0.117	¹³ C-1	0	0.735	
acetophenone- <i>d</i> ₂	-0.078			0.488	
acetophenone- <i>d</i> ₁	-0.039			0.244	
acetaldehyde- <i>d</i> ₃	-0.144 ^c	¹ H	<i>d</i>		
acetaldehyde- <i>d</i> ₂	-0.072 ^c			0.504	
acetaldehyde- <i>d</i> ₁				0.252	
acetic- <i>d</i> ₃ acid	-0.040			0.664	
acetic anhydride- <i>d</i> ₆	-0.050			0.675	
acetyl- <i>d</i> ₃ fluoride	-0.042	¹⁹ F	-0.0507		
acetyl- <i>d</i> ₂ fluoride		¹⁹ F	-0.0279		0.0233 ² ΔH(D)
acetyl- <i>d</i> ₁ fluoride	-0.014	¹⁹ F	-0.0109		0.0126 ² ΔH(D)
acetyl- <i>d</i> ₀ fluoride					0.02 ² ΔF(¹³ C)
propionyl- <i>d</i> ₂ fluoride	<i>e</i>	¹⁹ F	-0.100		
propionyl- <i>d</i> ₁ fluoride	<i>e</i>	¹⁹ F	-0.049		0.0154 ² ΔH(D)
methyl- <i>d</i> ₃ acetate	-0.030			0.667	
γ-butyrolactone- <i>d</i> ₂				0.584	0.191 ² ΔC _β (D)
γ-butyrolactone- <i>d</i> ₁				0.292	0.094 ² ΔC _γ (D)

^a In ppm. Defined as Δ = δC(H) - δC(D). ^b The isotopomers of acetone were prepared in a mixture. It is not possible experimentally to discern between isotopomers with the same number of deuterium. ^c Relative to acetaldehyde-*d*₁. ^d δCD₂HCHO - δCD₃CHO = -0.0008 ppm. ^e δCH₃CDHCOF - δCH₃CD₂COF = +0.007 ppm.

Table II. ³J(H,F) and ³J(D,F) in Acetyl Fluoride and Propionyl Fluoride

	CH ₃ CFO	CH ₂ DCFO	CHD ₂ CFO	CD ₃ CFO	CH ₃ CH ₂ CFO	CH ₃ CHDCFO	CH ₃ CD ₂ CFO
³ J(H,F)	7.0 ^a	6.76	6.5		0.3 ± 0.1	0.33 ± 0.1	
³ J(D,F)		1.12	1.07	1.06 ^b			nd

^a Has been reported in ref 15 as 7.6 Hz and in ref 16 as 7.0 Hz at -40 °C in SO₂ solution. ^b Given as 1.04 Hz in ref 16.

negative isotope effects in other systems³⁻⁸ and the apparent resemblance to hyperconjugation^{7,8} have spurred interest in unsaturated systems.⁹

The present investigation includes a number of simple carbonyl compounds such as acetone, acetaldehyde, acetophenone, and acetic acid and its derivatives acetyl fluoride, acetic anhydride, and methyl acetate, along with a few other simple compounds. All the compounds are to a varying extent tetrahedral at the α-carbon. Two types of isotope effects ²ΔCO(D) and ³ΔX(D), X being H, C, or F, are mainly of interest. The question of additivity of isotope effects is addressed through partially deuterated compounds. The choice of compounds with known geometry and use of information from spin-spin coupling constants permits the determination of the angular dependence of ³ΔF(D). In Figure 1 the preferred geometries of the investigated compounds are shown, as determined by microwave spectroscopy. The new data given in this work provides a better understanding of the isotope effect in unsaturated systems among which carbonium ions are of great interest. The data also lead us to suggest new ways of formulating the theoretical model for long-range isotope effects.

Results

The observed isotope effects on chemical shift and coupling constants respectively are collected in Tables I and II.

²ΔCO(D). The isotope effect over two bonds observed at the carbonyl carbon are in the cases of acetone, acetaldehyde, and acetyl fluoride seen to be additive when the data in Table I are

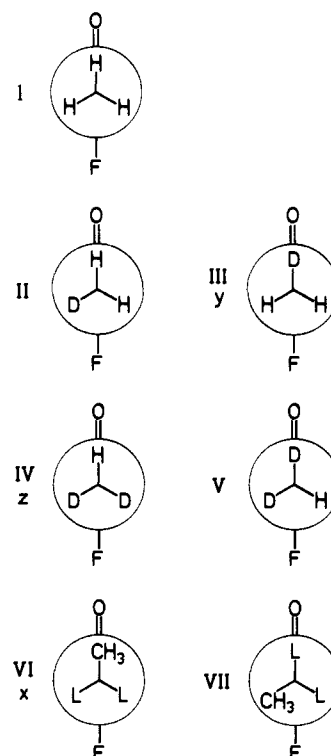


Figure 1. Rotamers used in the calculation of isotope effects. *x*, *y*, and *z* refer to the population of the rotamers III, IV, and VI appearing in eq 1-10 in the text. L symbolizes H or D.

inspected. For acetic acid and methyl acetate as well as acetic anhydride the isotope effects are so small that no measurable deviation from additivity can be expected, and they have accordingly not been investigated in these molecules. The small value of the isotope effect observed in the present work is in contrast

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to a previously published¹⁰ large value for acetic acid but in good agreement with observations reported for other acids.¹¹ In the present work several samples have been studied with different ratios of protio- and deuterioacetic acid in order to exclude the possible influence on the isotope effects from association equilibria.¹² The magnitude of the deuterium isotope effect per deuterium varies significantly among the compounds studied. From Table I it is seen that the effect decreases for the sequence acetaldehyde, acetone, acetophenone, acetyl fluoride, acetic anhydride, acetic acid, and methyl acetate.

³ΔF(D). The isotope effect over three bonds shows some interesting features. ³ΔF(D) is not additive in the case of acetyl fluoride, whereas it is perfectly additive in propionyl fluoride. The ³ΔH(D) is very small in the case of acetaldehyde, and the additivity could not be verified. In acetophenone ³ΔC(1)(D) is too small to be observed.

²ΔH(D). It can be noticed from Table I that ²ΔH(D) in acetyl fluoride is not strictly additive, although the deviation is small. The ²ΔH(D) observed for propionyl fluoride-*d*₁ differs slightly from that in acetyl-*d*₁ fluoride, indicating a small but detectable substituent effect of the methyl group. Such effects have also been seen in other aliphatic compounds.¹³

γ-Butyrolactone-β-*d* displays isotope effects over two bonds of measurable size ²ΔC_β(D) = 0.094 ppm and ²ΔC_γ(D) = 0.191 ppm for the mono- and dideuterated species.

A number of one-bond isotope effects has been determined in this work, as given in Table I. All ¹ΔC(D) are found to be additive.

In acetyl fluoride a single ²ΔF(¹³C) is measured. This effect is positive, small, and comparable to effects observed in fluoro-benzenes.¹⁴

Interpretation of Acetyl and Propionyl Fluoride Data. It is obvious, based on the results available in the literature^{15,16} that solvent and temperature play an important role, influencing measured values of ³J_{HF}. The results reported in this paper are based on experiments on sealed samples measured at approximately the same temperature. With this precaution the results found for ³J_{HF} and ³ΔF(D) in acetyl and propionyl fluoride may be interpreted in terms of rotational isomerism, as shown in the following equations:

CH₃COF:

$$J_t + 2J_g = 21.0 \quad (1)$$

CH₃CH₂COF:

$$J_t(1-x)/2 + J_g(1+x)/2 = 0.3 \quad (2)$$

CH₂DCOF:

$$J_t(1-y)/2 + J_g(1+y)/2 = 6.76 \quad (3)$$

CHD₂COF:

$$J_t z + J_g(1-z) = 6.50 \quad (4)$$

CD₃COF:

$$\Delta_t + 2\Delta_g = -0.0507 \quad (5)$$

CH₂D₂COF:

$$\Delta_t y + \Delta_g(1-y) = -0.0109 \quad (6)$$

CHD₂COF:

$$\Delta_t(1-z) + \Delta_g(1+z) = -0.0279 \quad (7)$$

CH₂D₂COF:

$$J_t y/6.51 + J_g(1-y)/6.51 = 1.12 \quad (8)$$

CHD₂COF:

$$J_t(1-z)/(2(6.51)) + J_g(1+z)/(2(6.51)) = 1.07 \quad (9)$$

CH₃CD₂COF:

$$\Delta_t(1-x)/2 + \Delta_g(1+3x)/2 = -0.1000 \quad (10)$$

where *J*_t and *J*_g are the trans and gauche ³J coupling constants and Δ_t and Δ_g the deuterium isotope effects from a deuterium located trans or gauche to fluorine.

The fractional population are specified by *x*, *y*, and *z* to signify (*x*) the population of CH₃ trans to fluorine in propionyl fluoride, (*y*) the population of D trans to fluorine in acetyl-*d*₁ fluoride, and (*z*) the population of H trans to fluorine in acetyl-*d*₂ fluoride.

From infrared and microwave spectroscopic measurements of propionyl fluoride, it is shown that the trans rotamer (form VI in Figure 1) has lower energy than the gauche isomer (form VII in Figure 1). The energy difference is determined to be 7.1 and 5.4 kJ/mol for the condensed¹⁷ and gas phase,¹⁸ respectively. The fractional population *x* for propionyl fluoride must therefore be expected to be significantly larger than 1/3.

For acetyl fluoride the fractional population *y* and *z* would normally be expected to be exactly 1/3. However, McKean¹⁹ has shown that the local methyl group geometry may differ significantly from C_{3v} point group symmetry in acetyl derivatives. For acetyl fluoride the most striking result of this fact is that the frequency for the CH stretching vibration is 45 cm⁻¹ higher in the trans position (to fluorine) than in the gauche position. This effect alone will introduce a difference between the zero-point vibrational energy for the two rotamers in acetyl-*d*₁ and acetyl-*d*₂ fluorides of ca. 7 cm⁻¹, resulting in a *small* preference for the configuration where deuterium is trans to fluorine. Other vibrational and/or solvent effects may increase (or decrease) the inequality of the rotamers of acetyl-*d*₁ fluoride and acetyl-*d*₂ fluoride. Rigorously, *J*_g, *J*_t, Δ_t, and Δ_g are not identical in the quoted eq 1-10—not even for acetyl fluoride—due to (intrinsic) isotope effects caused by different vibrational averaging in the individual isomers. However, in order to find a common (approximate) solution for eq 1-10, intrinsic isotope effects are neglected, and moreover it is assumed that Δ_t, Δ_g, *J*_t, and *J*_g are identical in acetyl fluoride and propionyl fluoride.

The 10 equations can be used to determine the 7 parameters with a nonlinear optimization program from the NAG subroutine library. The optimization has been performed with the sum of the squares of derivations as a quality function. Upper and lower bounds are introduced in accordance with programming needs and physical considerations.

It turns out that *x* is poorly determined by eq 1-10. Consequently the optimization has been performed for fixed *x* over a range of values consistent with the literature information.

The results are graphically represented in Figure 2. A consistent interpretation yields ³ΔF(D)_{trans} = 0.0618 ppm and ³ΔF(D)_{gauche} = -0.0555 ppm as well as populations *y* = 0.375 and *z* = 0.295 for the isotopomers of acetyl fluoride.

In the experimental data ³J_{HF} in propionyl fluoride is assumed to be positive. The use of a negative ³J_{HF} in eq 2 results in a less consistent solution of eq 1-10.

Discussion

³J_{HF} and Fractional Populations. The equations (1)-(10) define a solution which as seen in Figure 2 is dependent on the trans/gauche ratio in propionyl fluoride. The equation does not permit an independent evaluation of *x*. If the energy difference between the two rotamers Δ*E* taken from IR measurements is accepted as a reasonable estimate of the Δ*E* for the solutions used, a range of consistent results are found for each of the parameters. *J*_g is definitely small and negative while *J*_t is 23 ± 1 Hz. With the value Δ*E* = 7.1 kJ/mol, the estimate of the amount of gauche form in propionyl fluoride comes to 10%. The consistent values of ³J_g and

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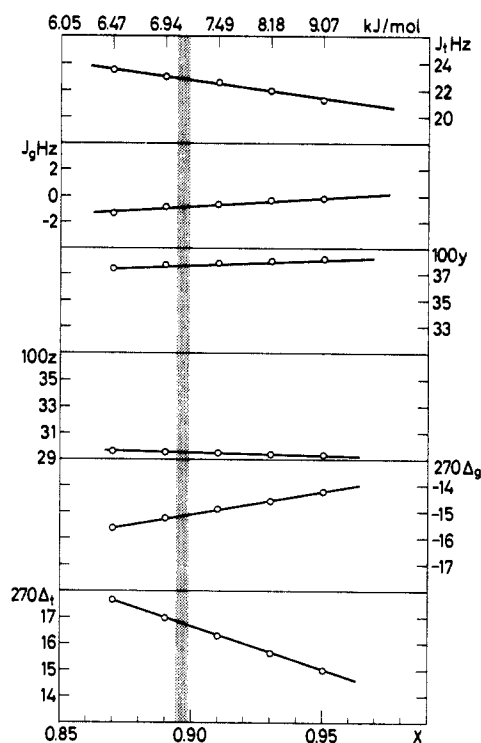


Figure 2. Graphical representation of the least-squares optimization determining spin-spin coupling constants, rotamer populations, and chemical shift isotope effects, based upon eq 1-10. The abscissa is given by the rotamer population VI in propionyl fluoride. The shaded region corresponds to the reported values from IR measurements in the condensed phase.¹⁷ The parameters have been scaled to be of similar magnitude. The accuracy of the solution has been probed by changing each of the measured values by $\pm 5\%$. On the basis of those calculations, the accuracy of the values is estimated as J_1 , ± 0.05 ; J_2 , ± 0.05 ; y , ± 0.01 ; $270\Delta_g$, ± 0.1 ; $270\Delta_i$, ± 0.5 .

3J_1 are -0.8 and 22.6 Hz. These values are smaller numerically than previous values published by Jones and Ladd¹⁵ in their work on substituted acetyl fluorides. Using the experimental microwave structure for acetyl fluoride,²⁰ we have calculated the CNDO/SOS values of $^3J_{HF}$ to be $^3J_{HF,trans} = 29.0$ Hz and $^3J_{HF,gauche} = 0.3$ Hz. The validity of this type of calculation is known to be limited,²¹ but in the present case the correspondence to the results of the optimization is rather good.

The values determined for the fractional populations y and z for acetyl- d_1 fluoride and acetyl- d_2 fluoride, respectively, are too far from $1/3$ to be explained from the difference in zero-point vibrational energy as mentioned above. However, the direction and relative magnitude is correct.

$^3\Delta F(D)$. Two features are conspicuous when the collected data are reviewed: (i) the negative sign and the nonadditivity in case of acetyl fluoride when contrasted to the additivity observed for propionyl fluoride, and (ii) the clear-cut conformational dependence as seen from $^3\Delta F(D)_{gauche} = -0.0555$ ppm and $^3\Delta F(D)_{trans} = 0.0618$ ppm. In principle the nonadditivity may be caused by two different factors: a change in the rotamer population as a result of the isotopic substitution, or a change of the intrinsic isotope effect when different numbers of deuterium atoms are incorporated. Very few cases are reported in the literature where the isotope effect intrinsically is nonadditive.¹ From the consideration of the $^3J_{HF}$ and $^3J_{DF}$ coupling constants, it was revealed that a slight difference in the rotamer populations exists in acetyl fluoride. It is therefore compelling to ascribe the nonadditivity to the perturbation of the rotamer equilibrium entirely. It is furthermore significant that the $^3\Delta F(D)$ observed in propionyl fluoride display additivity, in agreement with the fact that the preferred conformation (VI) is insensitive to deuterium substi-

tution. Forsyth et al.⁸ have used long-range deuterium isotope effects on ^{19}F shielding to gauge variations in the rotamer distribution of carbonium ions. The use of the $\cos^2 \theta$ relationship and hence positive isotope effects led to large deviations from equal rotamer populations. The introduction of unequal rotamer distribution does not fully account for the nonadditivity in our case. We therefore have to accept either that the use of a common set of $^3J_{HF}$ is less accurate than anticipated or that small variations in the intrinsic isotope effects occur in order to account for all information available from the experiments. A preliminary normal coordinate analysis shows that the CF stretching vibration mixes strongly with other modes, especially the C-C stretching and the CCH and HCH bending modes. The actual mixing of individual modes is strongly dependent on the degree of deuteration, which may be the origin of measurable intrinsic effects.

The determined values for $^3\Delta F(D)_{trans}$ and $^3\Delta F(D)_{gauche}$ are somewhat smaller than effects observed over three bonds in alicyclic compounds.^{22,23} This is not surprising since fluorine in the present case is bound to an sp^2 -hybridized carbon. In both studies $^3\Delta F(D)_{trans}$ is found to be more positive than $^3\Delta F(D)_{gauche}$.

$^2\Delta CO(D)$. The isotope effect over two bonds is found to be additive in all the compounds investigated. Intrinsic effects may occur, but they are smaller than the experimental error on the experimental observation. $^2\Delta CO(D)$ has been reported for a number of compounds. Morris and Murray³ found both positive and negative isotope effects in camphors, and Simpson and Stentzel⁴ report a conformational dependence of $^2\Delta CO(D)$. The gauche effect is of different magnitude than the trans effect. The reported behavior is similar to that of the $^3\Delta F(D)$ discussed above. That nonadditivity for acetyl fluoride has not been detected may be due to an accidental near coincidence of the values for the gauche and trans effects in this case. If both are positive, nonadditivity will be very difficult to observe when populations only differ a few percent from equal rotamer distribution.

The negative isotope effect observed for the carbonyl carbon cannot be explained in simple vibrational terms since all vibrational frequencies for groups directly linked to the CO carbon are reduced upon deuteration of the methyl group.

Forsyth et al.⁸ report a $^2\Delta C(D)$ in (phenyl- d_3)dimethylcarbonium ion of less than 10.091 Hz, which means an effect less than 0.015 ppm per deuterium. It can thus be argued that the effect decreases when the orbital is depleted. This reasoning might explain the decrease of the effect in the series acetaldehyde, acetone, acetophenone, acetyl fluoride, acetic anhydride, acetic acid, and methyl acetate. A parallel trend is observed for $^2\Delta C(D)$ in benzene derivatives, where the smallest effect is found at the carbon with the most electronegative substituents.²⁴

$^2\Delta H(D)$. The barely discernible nonadditivity of this effect is most likely caused by the unequal rotamer distribution, since the shielding caused by a C=O group positioned cis to a hydrogen is different from that of a C=O group in gauche position. Intrinsic effects as discussed for $^3\Delta F(D)$ can however not be ruled out based on the present experimental data.

Other Isotope Effects. The remaining isotope effects observed in this work are comparable to similar effects observed in other compounds and merit no further comments.

Experimental Section

Preparation of CH_3COF . The fluorinating agent 1,1,2-trifluoro-2-chloro-triethylamine (FR) was prepared following the procedure described by Schaumburg.²⁵ FR was distilled on a vacuum line prior to use.

CH_3COOH (2 mL, 99.9% purity Merck) was mixed with 5 mL of dry diethylene glycol diethyl ether in a flask with a magnetic stirrer and attached to a vacuum line. $(CH_3CO)_2O$ (0.1 mL) was distilled into the reaction mixture to remove traces of water. FR (7 mL) was subsequently distilled into the mixture cooled in liquid nitrogen. The reaction takes place when the liquid nitrogen is replaced by an ethanol bath with an initial temperature of 163 K. The reaction mixture is allowed gradually

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to reach room temperature over a period of 15 h under stirring. After the reaction is complete, the pressure over the reaction mixture is approximately 250 mmHg. CH_3COF is distilled from the reaction mixture placed in an ice bath into a flask on the vacuum line containing dry KF. This step ensures the removal of traces of HF produced during the reaction. CH_3COF is tested for purity by gas-phase IR spectroscopy. CH_3COF is distilled into an ampule stored at 253 K.

Preparation of CD_3COF . With the above described procedure, $\text{CD}_3\text{-COOD}$ (99.9% purity Merck) and $(\text{CD}_3\text{CO})_2\text{O}$ was used to prepare the substance.

Preparation of CH_2DCOF . Ketene was produced from $(\text{CH}_3\text{CO})_2\text{O}$ according to Bak et al.²⁶ on a vacuum line. The purified ketene was added to D_2O to produce CH_2DCOOD . An excess of ketene was maintained in order to ensure that the acetic acid produced was anhydrous. The preparation of the CH_2DCOF followed the procedure described above.

Preparation of CD_2HCOF . Dideuterioketene was produced from $(\text{CD}_3\text{CO})_2\text{O}$ following the procedures above, and CD_2HCOOH was converted to CD_2HCOF following the same procedure.

Preparation of $\text{CH}_3\text{CH}_2\text{COF}$. $\text{CH}_3\text{CH}_2\text{COOH}$ (2 mL, 99% purity Merck) was mixed with 10 mL of dry diethylene glycol diethyl ether in a flask on a vacuum line. FR (5 mL) was used in the procedure described above.

Preparation of $\text{CH}_3\text{CD}_2\text{COF}$. $\text{CH}_3\text{CH}_2\text{COONa}$ (2 g) was dissolved in 10 mL of D_2O , and the solution was placed in a glass ampule, which was sealed under vacuum. The ampule was placed in a water-filled steel tube that was closed with a pressure-tight lid. The assembly was heated to 440 K for 48 h. This treatment²⁷ resulted in the exchange of hydrogen to produce $\text{CH}_3\text{CD}_2\text{COONa}$. The salt was dried under vacuum and dissolved in diethylene glycol diethyl ether. Dry HCl gas was allowed to react with the solution for 2 h, whereafter the remaining HCl gas was pumped off. The solution of $\text{CH}_3\text{CD}_2\text{COOH}$ was used without further purification in the reaction with FR to produce $\text{CH}_3\text{CD}_2\text{COF}$.

Preparation of Deuterated Acetophenones. Mixtures of acetophenones PhCOCL_3 (L = H or D) were obtained by mixing appropriate amounts of acetophenone and acetophenone- d_3 (Stohler Isotope Chemicals). An exchange equilibrium was established within 30 min.

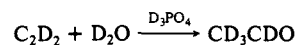
Preparation of Methyl- d_3 Acetate. Methyl- d_3 acetate was prepared by standard methods from acetyl chloride and methanol- d_4 .

Acetic acid and acetic anhydride- d_6 were commercial products from Stohler Isotope Chemicals and used without further purification.

Preparation of Deuterated Acetone. $(\text{CH}_3)_2\text{CO}$ (1 mL) and $(\text{CD}_3)_2\text{CO}$ (1 mL) were placed in a glass ampule and 1 mL of H_2O was added. The ampule was sealed and placed in a water-filled steel tube. The steel tube was closed pressure tight and heated for 24 h to 443 K. The partly deuterated acetone was dried over molecular sieve. Different H/D ratios were obtained by varying the amount of $(\text{CD}_3)_2\text{CO}$ and $(\text{CH}_3)_2\text{CO}$.

Preparation of Acetaldehyde- d_4 . D_3PO_4 (90% (w/w)) was prepared by the addition of D_2O to P_2O_5 . The acid (12 mL) was placed in a bulb connected to a vacuum line and evacuated. CaC_2 (6.5 g) was finely ground and placed in a two-necked bulb attached to the vacuum line and

fitted with a separation funnel containing 5 mL of D_2O . After evacuation, the D_2O was added to the CaC_2 to produce C_2D_2 , which was absorbed in the phosphoric acid. When the reaction



was completed, acetaldehyde was distilled from the reaction mixture into a dry ice cooled trap from where it was subsequently distilled into the NMR tube containing the solvent and reference compound. Partly deuterated acetaldehyde was obtained by using partly deuterated phosphoric acid.

Spectra. ^1H NMR spectra were obtained with a Bruker HX 270D spectrometer in Fourier transform mode. Samples were prepared by placing the solvent (CDCl_3 with 0.1% Me_4Si) in a 5-mm-o.d. sample tube with a glass joint. After attaching the tube to a vacuum line, the fluorides (or appropriate compounds) were distilled into the NMR tube. The tube was sealed under vacuum after several freeze-pump-thaw cycles. The tubes were stored at 253 K. The spectra were measured at 293 K with a spectral width of 1500 Hz and 32 K data points with zero filling to 64K before transformation. To improve resolution, Gaussian transformation has in some cases been applied.

^{19}F spectra were obtained with a Varian HA-100 spectrometer modified extensively with digital sweep and synthesizer-based frequency generation, permitting 10^{-3} Hz digitized resolution. The samples were measured under the conditions given above.

^{13}C spectra were obtained with a Bruker HX 270D spectrometer at 67.889 MHz. A spectral width of 3000–5000 Hz has been used with 64K data points. The samples were measured under the conditions given above.

The nonlinear optimization was performed with the program EO4KC from the NAG library (Numerical Algorithm Group, Oxford, UK).

Conclusion

The present study reveals that the isotope effects are usually additive but may in some cases be nonadditive. Nonadditivity is, however, not always observed because of coincidental cancellation. Furthermore isotope effects over three bonds, $^3\Delta\text{F(D)}$, show a marked orientational dependence. This dependence is clearly centered around the π -orbital of the carbonyl group, which makes the effects resemble hyperconjugation, a concept used to explain reactivities of similar organic compounds. The resemblance is, however, not a proof of a common origin. The effects must be discussed in terms of vibrational effects. It is not the intention of the present paper to go beyond the suggestions already made, but a future paper will deal more explicitly with an analysis based upon a complete analysis of the vibrational spectrum, including the fact that the barrier to rotation is low in some of these molecules, which may lead to a substantial change in the population of the low-lying energy levels upon deuteration.

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